Clinical trial results:
A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A

Summary

EudraCT number	2014-003880-38
Trial protocol	GB
Global end of trial date	14 February 2024

Results information

Result version number	v1 (current)
This version publication date	28 February 2025
First version publication date	28 February 2025
Summary attachment (see zip file)	BMN 270-201 Table screenshots (BMN 270-201 EudraCT Results_Table Screenshots.pdf)

Trial information

Trial identification

Sponsor protocol code	270-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02576795
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc
Sponsor organisation address	105 Digital Drive, Novato, CA, United States, 94949
Public contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., medinfo@bmrn.com
Scientific contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., medinfo@bmrn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2024
Global end of trial reached?	Yes
Global end of trial date	14 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess the safety of a single intravenous administration of a recombinant AAV5 encoding human coagulation FVIII (AAV5-hFVIII-SQ) vector.
- To determine the dose of AAV5-hFVIII-SQ required to achieve expression of hFVIII at or above 5% of normal activity (>=5 IU/dL) at 16 weeks after infusion. The kinetics, duration and magnitude of AAV-mediated hFVIII activity in individuals with hemophilia A were determined and correlated to an appropriate BMN 270 dose.

Protection of trial subjects:

This study was conducted in accordance with the following:

• European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, for studies conducted within any European country
• US Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable
• ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (ICH E6)

The study was conducted under a protocol reviewed and approved by an IEC and is conducted by scientifically and medically qualified persons. The benefits of the study were in proportion to the risks. The rights and welfare of the participants were respected and the investigators conducting the study did not find the hazards to outweigh the potential benefits.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 15
Worldwide total number of subjects	15
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 5 sites in United Kingdom (Basingstoke, Cambridge, Birmingham, Royal London, & Guys and St. Thomas's Trust, London).

Pre-assignment

Screening details:

21 subjects were screened.6 did not meet eligibility criteria for enrollment in study:5 were found to be adeno-associated virus5(AAV5)transduction inhibition(TI)/total antibody(TAb)+ve,&1 was assessed as being unable to comply with requirements of trial. 15 participants were enrolled were enrolled in 270-201 & received BMN 270 in 1 of 4 dose cohort

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BMN 270 6E12 vg/kg

Arm description:

Cohort 1: 6E12 vector genomes (vg) per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Arm type	Experimental
Investigational medicinal product name	Valacocogene Roxaparvovec
Investigational medicinal product code	BMN 270-201
Other name	AAV5-hFVIII-SQ/BMN 270
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

BMN 270 was infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs.

6E12 vector genomes (vg) per kilogram of body weight, given as a single intravenous dose (IV)

Arm title	BMN 270 2E13 vg/kg

Arm description:

Cohort 2: 2E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Arm type	Experimental
Investigational medicinal product name	Valacocogene Roxaparvovec
Investigational medicinal product code	BMN 270-201
Other name	AAV5-hFVIII-SQ/BMN 270
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

BMN 270 was infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs.

2E13 vg per kilogram of body weight, administered as a single intravenous dose (IV)

Arm title	BMN 270 4E13 vg/kg

Arm description:

Cohort 4: 4E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Arm type	Experimental
Investigational medicinal product name	Valacocogene Roxaparvovec
Investigational medicinal product code	BMN 270-201
Other name	AAV5-hFVIII-SQ/BMN 270
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

BMN 270 was infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs.

4E13 vg per kilogram, per kilogram of body weight, administered as a single intravenous dose (IV).

Arm title	BMN 270 6E13 vg/kg

Arm description:

Cohort 3: 6E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Arm type	Experimental
Investigational medicinal product name	Valacocogene Roxaparvovec
Investigational medicinal product code	BMN 270-201
Other name	AAV5-hFVIII-SQ/BMN 270
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

BMN 270 was infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs.

6E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

Number of subjects in period 1	BMN 270 6E12 vg/kg	BMN 270 2E13 vg/kg	BMN 270 4E13 vg/kg
Started	1	1	6
Completed	1	1	5
Not completed	0	0	1
Lost to follow-up	-	-	1

Number of subjects in period 1	BMN 270 6E13 vg/kg
Started	7

Completed	7
Not completed	0
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	BMN 270 6E12 vg/kg
Reporting group description:	
Cohort 1: 6E12 vector genomes (vg) per kilogram of body weight, given as a single intravenous dose (IV) valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A	
Reporting group title	BMN 270 2E13 vg/kg
Reporting group description:	
Cohort 2: 2E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV) valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A	
Reporting group title	BMN 270 4E13 vg/kg
Reporting group description:	
Cohort 4: 4E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV) valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A	
Reporting group title	BMN 270 6E13 vg/kg
Reporting group description:	
Cohort 3: 6E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV) valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A	

Reporting group values	BMN 270 6E12 vg/kg	BMN 270 2E13 vg/kg	BMN 270 4E13 vg/kg
Number of subjects	1	1	6
Age categorical			
Age at enrollment, n (%) Full Analysis Set (FAS): All enrolled participants who receive study drug and have at least one Baseline and post-Baseline assessment.			
Units: Subjects			
18 to < 40 years	1	0	5
40 to < 60 years	0	1	1
Gender categorical			
FAS population			
Units: Subjects			
Male	1	1	6
Race			
FAS population			
Units: Subjects			
Asian	1	0	0
Black or African American	0	0	1
White	0	1	5
Ethnicity			
FAS population.			
Units: Subjects			

Hispanic or Latino	0	0	0
Not Hispanic or Latino	1	1	6
Unknown or Not Reported	0	0	0
Baseline bleed counts (treated bleeds)			
FAS population			
Units: Subjects			
0 bleeds/year	0	0	1
> 0 to 4	1	1	2
> 4 to 10	0	0	0
> 10	0	0	3
History of previous diseases			
FAS population Liver Disease(LD) Some subjects may have multiple conditions. So the sum of subjects with HepB, HepC, HIV, LD and subjects without history of HepB/HepC/HIV/LD may not total to the overall number of subjects within the arm. In BMN 270-4E13 vg/kg Arm: 4 out of 6 subjects had no history of HepB/HepC/HIV/LD. One subject had multiple conditions (ie Hep B, Hep C and Liver Disease). Due to system limitation, it is reported as 2 in below table. In Total, 10 out of 15 subjects had no history of HepB/HepC/HIV/LD. Due to system limitations, it is showing as 8 in below table.			
Units: Subjects			
Hepatitis B	0	0	1
Hepatitis C	0	1	2
HIV	0	0	0
Liver disease	0	0	1
Subjects without History of HepB/HepC/HIV/LD	1	0	2
Number of target joints			
FAS population			
Units: Subjects			
n=0	0	0	3
n=1	0	0	1
n=2	0	1	0
n=3	1	0	0
n>3	0	0	2

Reporting group values	BMN 270 6E13 vg/kg	Total	
Number of subjects	7	15	
Age categorical			
Age at enrollment, n (%) Full Analysis Set (FAS): All enrolled participants who receive study drug and have at least one Baseline and post-Baseline assessment.			
Units: Subjects			
18 to < 40 years	6	12	
40 to < 60 years	1	3	
Gender categorical			
FAS population			
Units: Subjects			

Male	7	15	

Race			
FAS population			
Units: Subjects			
Asian	1	2	
Black or African American	0	1	
White	6	12	
Ethnicity			
FAS population.			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	7	15	
Unknown or Not Reported	0	0	
Baseline bleed counts (treated bleeds)			
FAS population			
Units: Subjects			
0 bleeds/year	1	2	
> 0 to 4	1	5	
> 4 to 10	1	1	
> 10	4	7	
History of previous diseases			
FAS population Liver Disease(LD) Some subjects may have multiple conditions. So the sum of subjects with HepB, HepC, HIV, LD and subjects without history of HepB/HepC/HIV/LD may not total to the overall number of subjects within the arm. In BMN 270-4E13 vg/kg Arm: 4 out of 6 subjects had no history of HepB/HepC/HIV/LD. One subject had multiple conditions (ie Hep B, Hep C and Liver Disease). Due to system limitation, it is reported as 2 in below table. In Total, 10 out of 15 subjects had no history of HepB/HepC/HIV/LD. Due to system limitations, it is showing as 8 in below table.			
Units: Subjects			
Hepatitis B	0	1	
Hepatitis C	2	5	
HIV	0	0	
Liver disease	0	1	
Subjects without History of HepB/HepC/HIV/LD	5	8	
Number of target joints			
FAS population			
Units: Subjects			
n=0	1	4	
n=1	3	4	
n=2	2	3	
n=3	0	1	
n>3	1	3	

End points

End points reporting groups

Reporting group title	BMN 270 6E12 vg/kg

Reporting group description:

Cohort 1: 6E12 vector genomes (vg) per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Reporting group title	BMN 270 2E13 vg/kg

Reporting group description:

Cohort 2: 2E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Reporting group title	BMN 270 4E13 vg/kg

Reporting group description:

Cohort 4: 4E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Reporting group title	BMN 270 6E13 vg/kg

Reporting group description:

Cohort 3: 6E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Primary: Number of Participants with Treatment-emergent Adverse Events

End point title	Number of Participants with Treatment-emergent Adverse Events[1]

End point description:

Adverse events (AEs) with onset or worsening after the investigational product were included. Participants with more than one AE of the same category were counted only once for that category.

Serious adverse event (SAE)

Safety analysis Population: The Safety analysis population was defined as all enrolled participants who received any amount of study drug.

End point type	Primary

End point timeframe:

Approximately Up to 7 years after dosing.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Subject incidence was summarized descriptively in each reporting groups.

End point values	BMN 270 6E12 vg/kg	BMN 270 2E13 vg/kg	BMN 270 4E13 vg/kg	BMN 270 6E13 vg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	6	7
Units: Participants				
number (not applicable)				
Participants with any AE	1	1	6	7
AEs leading to dose adjustment during infusion	0	0	0	0
AEs leading to dose interruption during infusion	0	0	0	0
AEs leading to study drug discontinuation	0	0	0	0
Participants with any SAE	1	0	3	5
Participants with any treatment-related AE	1	0	6	7
Treatment-related SAEs	0	0	1	0
Participants with any AE of Grade >= 3	1	1	1	2
Participants who died	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participant with Median FVIII Activity Levels >=5 IU/dL Using Chromogenic Substrate Assay (CSA)

End point title	Number of Participant with Median FVIII Activity Levels >=5 IU/dL Using Chromogenic Substrate Assay (CSA)[2]

End point description:

Responder/Non responder status, where a responder was defined as a participant with median FVIII activity of >= 5 IU/dL during Week 13-16 post-BMN 270 infusion.

FAS Population

End point type	Primary

End point timeframe:

Week 13-16 post-BMN 270 infusion

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Incidence of subject defined in the endpoint was summarized descriptively in each reporting groups.

End point values	BMN 270 6E12 vg/kg	BMN 270 2E13 vg/kg	BMN 270 4E13 vg/kg	BMN 270 6E13 vg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	6	7
Units: participants				
number (not applicable)	0	0	5	7

Statistical analyses

No statistical analyses for this end point

Primary: Median FVIII Activity as Measured by Chromogenic Substrate Assay During Week 13-16 Post-BMN 270 Infusion

End point title	Median FVIII Activity as Measured by Chromogenic Substrate Assay During Week 13-16 Post-BMN 270 Infusion[3]

End point description:

Values for FVIII activity were excluded from analysis if obtained within 72 hours since the last infusion of exogenous FVIII replacement therapy

FVIII activity levels below the Lower limit of quantitation (LLOQ) will be imputed with 0 IU/dL

Q1: 25% Percentile; Q3: 75% Percentile

FAS Population

Neither participant in either the 6E12 vg/kg or 2E13 vg/kg cohort reached ≥ 5 IU/dL as of Weeks 13-16. Hence, these arms are not included for this endpoint.

Efficacy results in this section are presented by dose cohort, with a primary focus on the 6E13 vg/kg and 4E13 vg/kg dose cohorts. One participant was dosed in each of the two lowest dose cohorts (6E12 vg/kg and 2E13 vg/kg) as part of the dose escalation scheme in Part 1 of the study. Neither participant showed an appreciable FVIII response following BMN 270 dosing at these dose levels

End point type	Primary

End point timeframe:

Week 13-16 post-BMN 270 infusion

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: FVIII activity was summarized descriptively in each reporting groups.

End point values	BMN 270 6E12 vg/kg	BMN 270 2E13 vg/kg	BMN 270 4E13 vg/kg	BMN 270 6E13 vg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	6	7
Units: IU/dL				
median (inter-quartile range (Q1-Q3))	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	16.30 (11.05 to 19.90)	50.40 (31.30 to 64.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate Requiring Exogenous Factor VIII Replacement Treatment during Week 5 and Beyond

End point title	Annualized Bleeding Rate Requiring Exogenous Factor VIII Replacement Treatment during Week 5 and Beyond[4]

End point description:

ABR= [Number of bleeding episodes during calculation period] / [Total number of days during the calculation period] ×365.25

A bleeding episode (treated) was defined as a bleed or symptoms associated with the development of a bleed (or multiple bleeds occurring in the same day) requiring FVIII replacement treatment within 72 hours of the start of the bleed.

The baseline values for the secondary efficacy endpoints were based on the historical data prior to study

enrollment.

Annualized bleeding rate (ABR)

FAS Population

End point type	Secondary

End point timeframe:

Week 5 and Beyond (approximately 7 years post Infusion).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy results in this section are presented by dose cohort, with a primary focus on the 6E13 vg/kg and 4E13 vg/kg dose cohorts. One participant was dosed in each of the two lowest dose cohorts (6E12 vg/kg and 2E13 vg/kg) as part of the dose escalation scheme in Part 1 of the study. Neither participant showed an appreciable FVIII response following BMN 270 dosing at these dose levels.

End point values	BMN 270 4E13 vg/kg	BMN 270 6E13 vg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: bleeds/year				
arithmetic mean (standard deviation)				
ABR at Week 5 and Beyond	1.58 (± 1.97)	0.75 (± 1.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Factor VIII Utilization during Week 5 and Beyond

End point title	Annualized Factor VIII Utilization during Week 5 and Beyond[5]

End point description:

Annualized FVIII use (IU/kg/yr.) =[Sum of FVIII use (IU/kg) during calculation period] / [Total number of days during the calculation period] ×365.25

FAS Population

End point type	Secondary

End point timeframe:

Week 5 and Beyond (approximately 7 years post Infusion)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy results in this section are presented by dose cohort, with a primary focus on the 6E13 vg/kg and 4E13 vg/kg dose cohorts. One participant was dosed in each of the two lowest dose cohorts (6E12 vg/kg and 2E13 vg/kg) as part of the dose escalation scheme in Part 1 of the study. Neither participant showed an appreciable FVIII response following BMN 270 dosing at these dose levels.

End point values	BMN 270 4E13 vg/kg	BMN 270 6E13 vg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: IU/kg/yr				
arithmetic mean (standard deviation)				

Annualized FVIII Usage at Week 5 and Beyond	331.65 (± 360.19)	228.72 (± 311.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Factor VIII Infusion Rate during Week 5 and Beyond

End point title	Annualized Factor VIII Infusion Rate during Week 5 and Beyond[6]

End point description:

Annualized FVIII infusion rate (count/yr.) = [Number of FVIII replacement infusions during calculation period] / [Total number of days during the calculation period] ×365.25

FAS population

End point type	Secondary

End point timeframe:

Week 5 and Beyond (approximately 7 years post Infusion)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Efficacy results in this section are presented by dose cohort, with a primary focus on the 6E13 vg/kg and 4E13 vg/kg dose cohorts. One participant was dosed in each of the two lowest dose cohorts (6E12 vg/kg and 2E13 vg/kg) as part of the dose escalation scheme in Part 1 of the study. Neither participant showed an appreciable FVIII response following BMN 270 dosing at these dose levels.

End point values	BMN 270 4E13 vg/kg	BMN 270 6E13 vg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: Infusions/ year				
arithmetic mean (standard deviation)				
Annualized FVIII infusion rate Week 5 and Beyond	10.25 (± 9.06)	6.38 (± 8.19)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately up to 7 years after dosing.

Adverse event reporting additional description:

AEs with onset or worsening after the investigational product were included

Subjects with more than one AE of the same PT were counted only once for that Preferred term (PT)

AEs were graded for severity using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version v4.03

Safety analysis Population

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	BMN 270 6E12 vg/kg

Reporting group description:

Cohort 1: 6E12 vector genomes (vg) per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Reporting group title	BMN 270 2E13 vg/kg

Reporting group description:

Cohort 2: 2E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Reporting group title	BMN 270 4E13 vg/kg

Reporting group description:

Cohort 4: 4E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Reporting group title	BMN 270 6E13 vg/kg

Reporting group description:

Cohort 3: 6E13 vg per kilogram, per kilogram of body weight, given as a single intravenous dose (IV)

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A

Reporting group title	Overall

Reporting group description:

Valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A.

Serious adverse events	BMN 270 6E12 vg/kg	BMN 270 2E13 vg/kg	BMN 270 4E13 vg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	3 / 6 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acinic cell carcinoma of salivary gland			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery dissection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rectal haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemophilic arthropathy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint stiffness			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BMN 270 6E13 vg/kg	Overall	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	9 / 15 (60.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acinic cell carcinoma of salivary gland			

subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery dissection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemophilic arthropathy			

subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint stiffness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	BMN 270 6E12 vg/kg	BMN 270 2E13 vg/kg	BMN 270 4E13 vg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acinic cell carcinoma of salivary gland			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemangioma of liver			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemangioma of skin			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Melanocytic naevus			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Hangover			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Puncture site swelling			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	2
Swelling			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vaccination site pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Immune system disorders			
Allergy to animal			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Epididymal cyst			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sexual dysfunction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	2 / 6 (33.33%)
occurrences (all)	0	1	3
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Productive cough			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Snoring			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Euphoric mood			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Panic attack			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	5 / 6 (83.33%)
occurrences (all)	2	0	8
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	5 / 6 (83.33%)
occurrences (all)	1	0	5
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood urine present			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Coagulation factor VIII level decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Coagulation factor VIII level increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Thrombin time prolonged			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Foot fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Head injury			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint dislocation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Limb injury			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Post procedural haemorrhage			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Post-traumatic pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Thermal burn			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tooth fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Traumatic haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Aura			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Carotid artery dissection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	3 / 6 (50.00%)
occurrences (all)	1	0	34
Hypoaesthesia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Loss of consciousness			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	3
Parosmia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sleep deficit			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Syncope			

subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Typical aura without headache			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Neutrophilia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Splenomegaly			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Thrombocytosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
External ear inflammation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Eyelid oedema			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Scleral discolouration			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Colitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Crohn's disease			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Diarrhoea			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Dyspepsia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Inguinal hernia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Hepatitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hepatomegaly			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Actinic keratosis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Eczema			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Idiopathic guttate hypomelanosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Leukoderma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Purpura			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Rosacea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin disorder			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin reaction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin striae			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Polyuria			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Renal colic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal cyst			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	5 / 6 (83.33%)
occurrences (all)	2	1	9
Arthritis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Arthropathy			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	3 / 6 (50.00%)
occurrences (all)	6	1	5
Back pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	6
Bursitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Haemophilic arthropathy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Joint range of motion decreased			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Joint stiffness			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Joint swelling			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Neck mass			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Rotator cuff syndrome			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Synovitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Conjunctivitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Diarrhoea infectious			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Epididymitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Epstein-Barr virus infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Fungal skin infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Furuncle			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	3 / 6 (50.00%)
occurrences (all)	1	3	4
Oral herpes			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pericoronitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Pharyngitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	3
Sputum purulent			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tinea infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	2 / 6 (33.33%)
occurrences (all)	2	1	2
Viral infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Viral pharyngitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Increased appetite			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Polydipsia			

subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	BMN 270 6E13 vg/kg	Overall	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	15 / 15 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acinic cell carcinoma of salivary gland			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Haemangioma of liver			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Haemangioma of skin			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Melanocytic naevus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)	2 / 15 (13.33%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
Fatigue			

subjects affected / exposed	3 / 7 (42.86%)	6 / 15 (40.00%)	
occurrences (all)	4	7	
Hangover			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Influenza like illness			
subjects affected / exposed	1 / 7 (14.29%)	4 / 15 (26.67%)	
occurrences (all)	1	4	
Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Puncture site swelling			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	4 / 15 (26.67%)	
occurrences (all)	2	5	
Swelling			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Vaccination site pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Immune system disorders			
Allergy to animal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	2 / 7 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	3	4	
Reproductive system and breast disorders			
Epididymal cyst			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Sexual dysfunction			

subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 7 (42.86%)	6 / 15 (40.00%)	
occurrences (all)	5	9	
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 7 (14.29%)	4 / 15 (26.67%)	
occurrences (all)	2	5	
Productive cough			
subjects affected / exposed	2 / 7 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	2	3	
Snoring			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 7 (28.57%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Depressed mood			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Euphoric mood			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Insomnia			

subjects affected / exposed	3 / 7 (42.86%)	4 / 15 (26.67%)	
occurrences (all)	3	4	
Panic attack			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 7 (100.00%)	13 / 15 (86.67%)	
occurrences (all)	9	19	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 7 (42.86%)	9 / 15 (60.00%)	
occurrences (all)	4	10	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 7 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	2	3	
Blood urine present			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Coagulation factor VIII level decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Coagulation factor VIII level increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Thrombin time prolonged			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Weight increased			
subjects affected / exposed	2 / 7 (28.57%)	2 / 15 (13.33%)	
occurrences (all)	4	4	
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	2 / 7 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	2	3	
Foot fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Head injury			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Joint dislocation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Joint injury			
subjects affected / exposed	2 / 7 (28.57%)	2 / 15 (13.33%)	
occurrences (all)	5	5	
Ligament sprain			
subjects affected / exposed	1 / 7 (14.29%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Limb injury			
subjects affected / exposed	2 / 7 (28.57%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Muscle strain			

subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Post procedural haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Post-traumatic pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Procedural pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Thermal burn			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Traumatic haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Nervous system disorders			
Aura			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	3	3	
Carotid artery dissection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Headache			
subjects affected / exposed	4 / 7 (57.14%)	8 / 15 (53.33%)	
occurrences (all)	10	45	
Hypoaesthesia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	

Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Loss of consciousness			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Migraine			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	12	12	
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 15 (20.00%)	
occurrences (all)	1	5	
Parosmia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Sleep deficit			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Typical aura without headache			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Iron deficiency anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	3	
Neutrophilia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Splenomegaly			

subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Thrombocytosis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Ear pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
External ear inflammation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	5	
Eyelid oedema			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Photophobia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Scleral discolouration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Colitis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Crohn's disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	4 / 7 (57.14%)	6 / 15 (40.00%)	
occurrences (all)	7	11	
Dyspepsia			
subjects affected / exposed	2 / 7 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	2	3	
Dysphagia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Inguinal hernia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 7 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	4	5	
Rectal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	2 / 7 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	4	5	
Vomiting			
subjects affected / exposed	4 / 7 (57.14%)	5 / 15 (33.33%)	
occurrences (all)	7	8	
Hepatobiliary disorders			

Hepatic steatosis			
subjects affected / exposed	1 / 7 (14.29%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Hepatitis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Hepatomegaly			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 7 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	2	3	
Actinic keratosis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Eczema			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Hyperhidrosis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	2	
Idiopathic guttate hypomelanosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Leukoderma			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Purpura			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 7 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Rosacea			

subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Skin disorder			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Skin reaction			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Skin striae			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Renal colic			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Renal cyst			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 7 (85.71%)	13 / 15 (86.67%)	
occurrences (all)	16	28	
Arthritis			

subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Arthropathy			
subjects affected / exposed	2 / 7 (28.57%)	7 / 15 (46.67%)	
occurrences (all)	4	16	
Back pain			
subjects affected / exposed	3 / 7 (42.86%)	6 / 15 (40.00%)	
occurrences (all)	4	10	
Bursitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Haemophilic arthropathy			
subjects affected / exposed	2 / 7 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	2	3	
Joint range of motion decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Joint stiffness			
subjects affected / exposed	0 / 7 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Joint swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	2	3	
Neck mass			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pain in extremity			

subjects affected / exposed	5 / 7 (71.43%)	6 / 15 (40.00%)	
occurrences (all)	5	8	
Rotator cuff syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Synovitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 7 (14.29%)	4 / 15 (26.67%)	
occurrences (all)	1	4	
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Diarrhoea infectious			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Ear infection			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	2	3	
Epididymitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Epstein-Barr virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Fungal skin infection			
subjects affected / exposed	2 / 7 (28.57%)	2 / 15 (13.33%)	
occurrences (all)	3	3	

Furuncle			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Hordeolum			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Lower respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	2	3	
Nasopharyngitis			
subjects affected / exposed	5 / 7 (71.43%)	10 / 15 (66.67%)	
occurrences (all)	8	16	
Oral herpes			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Pericoronitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Pharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	4	4	
Rhinitis			
subjects affected / exposed	1 / 7 (14.29%)	4 / 15 (26.67%)	
occurrences (all)	1	6	
Sputum purulent			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Tinea infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Tonsillitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	

Upper respiratory tract infection			
subjects affected / exposed	2 / 7 (28.57%)	6 / 15 (40.00%)	
occurrences (all)	3	8	
Viral infection			
subjects affected / exposed	1 / 7 (14.29%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Viral pharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	4	
Increased appetite			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Iron deficiency			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Polydipsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	1 / 7 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2015	Amendment 1: 1. Receipt of any vector or gene transfer agent was added to the exclusion criteria. 2. The inclusion criterion definition of "severe" was changed from "FVIII levels have ever declined to 1 IU/dL or less" to a "FVIII baseline level is 1 IU/dL or less".
26 May 2015	Amendment 2: 1. HIV positive patients and patients with any evidence of active infection or any immunosuppressive disorder were excluded from the study. 2. Study stopping criteria were changed to temporarily stop enrollment when triggered, rather than allowing enrollment to continue while additional analyses were performed. 3. Requirement of a FVIII Treatment Washout period was removed.
06 November 2015	Amendment 3: 1. Changes to participant management, including the use of prophylactic CS, were made in the event that a participant develops ALT elevated 1.5x above his baseline after BMN 270 dosing. 2. Planned major surgery during the 16-week period following BMN 270 infusion was added as an exclusion criterion. 3. To reduce participant burden and limit blood volume requirements, a “smart rescreening” option was added for participants who are successfully screened but did not undergo Baseline assessments and Infusion within the 28 + 14 day window required by the protocol.

02 September 2016	Amendment 4: 1. The requirement for prophylactic CS was removed, and the threshold for starting reactive CS has been changed from ALT >= 1.5x baseline value to >= 1.5x ULN 2. Cohort 4 was added to the study 3. The enrollment stopping criterion related to serum ALT levels has been changed from a 5-fold increase from baseline after BMN 270 administration to: ALT elevation > 5x ULN for at least 2 consecutive weeks after administration of BMN 270 in the absence of a definitive alternate etiology for the increase. 4. Changes to the frequency of vector shedding assessments were made (less frequently before Week 16, more frequently after Week 16). 5. The enrollment stopping criterion around vector shedding was modified. Enrollment in the study was to be halted if there is persistent detection (defined as 3 consecutive positive samples) of AAV vector DNA in the semen of a participant more than 52 weeks after BMN 270 administration. 6. Stopping criterion regarding Grade 2 related events has been changed to trigger a DRB review of safety data to determine whether an enrollment halt is warranted, rather than triggering an automatic enrollment halt. 7. Testing of von Willebrand factor antigen was added. 8. Testing of creatine phosphokinase (CPK) was added to routine blood chemistry assessments. 9. An exploratory Direct Thrombin assay was added.
14 February 2017	Amendment 5: 1. Frequency of local laboratory testing of ALT and FVIII during Weeks 1-20 was reduced. 2. The frequency of PBMC collection was increased. 3. Participants are now required to continue to provide semen samples for PCR analysis through Week 12, even if they have already had 3 consecutive negative results in semen prior to that timepoint. 4. Language was added to allow exploratory fractionation of collected samples (such as plasma, PBMCs, and red blood cells).
21 December 2017	Amendment 6: 1. The frequency of liver function and FVIII testing was increased during the Years 2-5 follow-up period. Testing will be performed every 4 weeks (+ 2 weeks) during Year 2, and every 6 weeks (± 2 weeks) during years 3-5. 2. Exploratory biomarker sampling was extended beyond Week 24 to permit further analysis of exploratory endpoints during the study.

10 October 2018	Amendment 7: 1. Efavirenz, lamivudine, and experimental hemophilia treatments (emicizumab, fitusiran, and concizumab) were added to the prohibited concomitant medications. 2. ABO testing was added. 3. Participants are being advised to abstain from blood or sperm donation after BMN 270 infusion until there is no further evidence of vector shedding. 4. Twice weekly evaluation of liver tests (LTs) was added during times when a participant's ALT is >= 3x ULN. 5. An abbreviated visit schedule was made available during Years 2-5 for participants who are considered to have not responded to BMN 270 therapy to reduce participant burden in participants who had not achieved FVIII activity at least 5 IU/dL by Week 52. 6. Language concerning when to consider restarting FVIII prophylaxis following BMN 270 infusion was modified to emphasize that the decision should be made on clinical grounds (eg, bleeding episodes) rather than on FVIII activity levels.
31 January 2019	Amendment 8: 1. An optional liver biopsy substudy was added to the protocol.
19 June 2020	Amendment 9: 1. The duration of the study was extended from 5 years to 7 years post-infusion. 2. Language was added to permit the use of mobile nursing (MN) services, provided that the participant consents and that the site can implement the use of such services. 3. Lamivudine was removed as a prohibited medication. 4. The occurrence of events of Hy's law was added as an event of special interest (EOSI) for purposes of expedited safety reporting. 5. The development of anti-FVIII inhibitory antibodies (inhibitors) was added as an EOSI for purposes of expedited safety reporting. 6. Language was added concerning the use of liver biopsy sample information from samples collected outside of the liver biopsy substudy. 7. Vector shedding and contraception use language was updated to change the determination of a "clear" result from negative to below the limit of detection, to better reflect regulatory guidance and to align 270-201 with other studies in the BMN 270 program. 8. Given possible travel and site restrictions caused by COVID-19, language was added to allow an investigator to document verbal confirmation by a participant that has signed and dated the written informed consent when the investigator cannot obtain a copy of the signed informed consent prior to initiating study procedures.

24 August 2021	Amendment 10: 1. Changes were made to enhance screening for potential malignancies (including hepatic cancers) after dosing with BMN 270. 2. Malignancy (except non-melanoma skin cancer) was added as an EOSI. 3. Language was added concerning the use of the SARS-CoV-2 vaccines. 4. Guidance concerning the use of reactive CS for ALT elevations was updated. 5. The definition of treatment failure was changed. 6. Frequency of several laboratory assessments after Year 1 was decreased: • FVIII Antigen BDD Assay reduced to Q12W after Year 1 through Year 5, and Q26W in Years 6-7. • AAV5 TAb reduced to End of Year Visits only after Year 1 • FVIII TAb reduced to End of Year Visits only after Year 1

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported